



## **Analysis of chromosomal abnormalities as a possible cause of Multiple Sclerosis**

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### **Summary**

Chromosomal abnormalities that affect either entire chromosomes or large chromosomal regions covering multiple genes are capable of profoundly affecting human health, as in the case of Down syndrome (caused by trisomy 21) and Burkitt's lymphoma (caused by a chromosomal translocation). Therefore, these types of defects must be included in our analysis of possible genetic causes of multiple sclerosis.

A review of the literature on this topic indicates that MS is almost certainly not caused by an inherent chromosomal abnormality as in the case of Down syndrome. On the other hand, somatic chromosomal aberrations have been found at higher frequencies of cells of people with MS than in controls, but the significance of this phenomenon is not yet understood.

### **Hypothesis**

Chromosomal abnormalities (congenital or somatic) either cause MS or influence susceptibility to MS.

### **Experimental tests of the hypothesis**

Several studies have examined chromosomal integrity in patients with MS<sup>1-6</sup>. These studies for the most part report an increased incidence of breaks, gaps, rearrangements, etc. in the chromosomes of MS patients compared to controls. One study found particularly increased levels of abnormalities in patients with a high relapse rate or a progressive form of MS<sup>4</sup>. A different study<sup>5</sup> found an increased incidence of anomalies in CSF lymphocytes but not in peripheral blood lymphocytes (PBLs), although other studies that examined PBLs did find increases in those cells. One research group determined that there was no difference in the spontaneous occurrence of chromatid breaks in blood cells between secondary progressive MS subjects and healthy individuals, but did find an increased frequency of multinucleated cells in MS subjects<sup>6</sup>.

The sister chromatid exchange (SCE)<sup>\*</sup> assay has also been used in multiple experiments to assess chromosomal damage in MS. SCE levels were found in six studies to be

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<sup>\*</sup> "The sister chromatid exchange (SCE) assay provides a sensitive means for evaluating cytogenetic damage caused by chemical or physical agents. Chemical mutagens often induce SCEs at concentrations which are lower than those required to produce significant yields of

increased in MS patients compared to controls<sup>7-12</sup>. One study found an increased SCE rate only in sporadic cases of MS, not in familial cases<sup>9</sup>.

Other experiments have taken the next step of investigating the underlying basis for the chromosomal damage seen in people with MS. It is of interest to know whether such damage contributes to the initial development of MS or whether it is a result of events taking place during the course of the disease. Two studies examined the potential clastogenic effect of azathioprine, an immunosuppressive chemotherapy drug, in MS patients; the results were contradictory<sup>1,2</sup>. Similarly, cellular radiosensitivity was explored in three studies. One found it to be enhanced in people with MS<sup>13</sup>, a second did not<sup>7</sup>, and the third, which used a G0 low-dose radiation micronucleus assay, found that cells in MS patients actually had enhanced radioresistance<sup>6</sup>. The authors of this last study speculated that adaptation to oxidative stress may help protect people with MS against further DNA damage. Another study found the intrinsic DNA repair capability of people with MS to be unimpaired<sup>14</sup>, suggesting that an exogenous factor causes chromosomal instability in MS. Finally, the presence of a particular oxidative marker was found to be elevated in MS plaques and surrounding white matter compared with control tissue; the authors suggested that permanent degeneration may be due to DNA damage caused by oxidative compounds released during the inflammatory process<sup>15</sup>.

With respect to specific chromosomal locations, an MS-susceptibility gene locus on chromosome 17 has been found to be flanked by palindromic stretches of DNA and long homologous duplications present at each end of the MS-related haplotype. Such sequences have been linked with genomic instability, raising the possibility that chromosomal alterations at this locus may contribute to the risk of MS<sup>16</sup>. In another study based on a publication search for comorbidities, it was postulated that trisomy 21, or Down Syndrome, actually may protect against MS<sup>17</sup>. There have been no other studies to verify this or elucidate why the extra genetic information in the superfluous chromosome may protect the body from MS.

## Conclusions

Based on the results of the several cytogenetic studies conducted to date, MS is presumably not caused by or associated with the inheritance of significant chromosomal abnormalities such as monosomy, trisomy, triploidy, partial trisomy or monosomy, ring chromosomes, or Robertsonian translocations. It is reasonable to expect that such major defects, if consistently present in cells of people with MS, would have been identified in some or all of these studies. Large deletions or insertions spanning multiple genes presumably also would have been identified via cytogenetic analysis or through one of the genome-wide scans that have been conducted in MS.

Experimental evidence does, however, suggest that *somatic* chromosomal aberrations are found at a higher frequency in the cells of people with MS than in those of controls. Multiple studies have found increased incidences of chromosomal aberrations such as

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chromosomal aberrations. When cells are treated with compounds that cause lesions which persist through cell division, exchanges will occur between the daughter chromatids. Chromosomes are treated so that the two sister chromatids can be differentially stained." (From [www.litronlabs.com/sister-chromatid-exchange.htm](http://www.litronlabs.com/sister-chromatid-exchange.htm).)

breaks, gaps, translocations, dicentric chromosomes, chromatid exchange figures, and deletions in MS patients when compared with controls.

It is unclear at this time what role somatic chromosomal abnormalities play in the etiology or pathogenesis of MS, due in large part to the insufficient number of studies conducted in this area. The available evidence from the few experiments that have been performed is mixed on the subject of what the fundamental cause of MS-associated chromosomal anomalies might be. Nor does the evidence clearly distinguish whether DNA damage contributes to MS susceptibility or is simply a result of the disease process, with or without deleterious consequences of its own further downstream. One study speculates that DNA damage resulting from inflammatory oxidation contributes to irreversible neurodegeneration<sup>15</sup>. Another analysis hypothesizes that translocations or other chromosomal defects in certain B cells causes these cells to clonally proliferate, resulting in the oligoclonal bands seen in the CSF of MS patients<sup>18</sup>.

It is interesting to note that similar questions concerning the role of somatic chromosomal anomalies exist for other diseases as well. For example, various chromosomal abnormalities, most notably trisomy 7, have been found in the synovial fibroblasts of patients with rheumatoid arthritis; however, the role and significance of these anomalies are still under debate<sup>19-22</sup>.

Further research is needed to elucidate the nature of the association between somatic chromosomal abnormalities and MS: are these defects a causal factor for MS or do they result from events taking place during the course of MS? In addition, if chromosomal defects are partly responsible for the development of MS, are these defects due to a genetic predisposition to chromosomal damage or to an environmental factor that results in chromosomal damage? Follow-on studies – preferably involving larger sample sizes than those cited in these papers – may eventually lead to a successful resolution of these questions.

## References

- 1 I. Unglaub-Leisten, H. Stickl, E. Frick, H. Angstwurm and J. Ring, [*Chromosomal aberrations in peripheral lymphocytes of patients with multiple sclerosis (author's transl)*]. Dtsch Med Wochenschr, 1975. **100**(40): p. 2028-34. PubMed ID: 1157719.  
Structural aberrations (breaks and gaps) in chromosomes of peripheral lymphocytes in 35 MS patients treated with azathioprine, antilymphocytic globulin or thoracic-duct drainage were found at a higher rate than in controls. Aberrations were also increased in untreated patients, but at a lower level. B and C chromosomes of azathioprine-treated patients were more frequently involved, as was the terminal segment of the long arm of chromosome 1. In all groups there was an increase in aberrations in the center of the long arm of the C-chromosome.
- 2 F. Apelt, J. Kolin-Gerresheim and M. Bauchinger, *Azathioprine, a clastogen in human somatic cells? Analysis of chromosome damage and SCE in lymphocytes after exposure in vivo and in vitro*. Mutat Res, 1981. **88**(1): p. 61-72. PubMed ID: 6163078.

Azathioprine was found not to be clastogenic. 28 MS patients before and after treatment both had a higher incidence of gaps compared with controls. In addition, treatment of cultured lymphocytes did not yield increased SCE frequencies.

- 3 W. Vormittag, E. Maida, A. Totseva, E. Kunze-Muhl and K. Summer, [*Multiple sclerosis and chromosomal aberrations (author's transl)*]. Wien Klin Wochenschr, 1981. **93**(23): p. 724-9. PubMed ID: 6979129.

The incidence of peripheral lymphocytes with chromosomal breaks in 35 female MS patients was measured at 2.0% compared with 1.1% in 25 healthy female controls ( $p < 0.01$ ). Chromosomal rearrangements (dicentric chromosomes, translocation chromosomes, chromatid exchange figures) were also observed more frequently in patients vs. controls. A relative surplus of breaks was found in chromosome A2 and D-group chromosomes.

- 4 E. D'Alessandro, M. Di Cola, M. L. Lo Re, C. Ligas, C. Vaccarella, F. D'Andrea, C. Marini and M. Prencipe, *Nonrandom chromosome changes in multiple sclerosis*. Am J Med Genet, 1990. **37**(3): p. 406-11. PubMed ID: 2260573.

Cytogenetic analysis of 48 patients with clinically definite MS showed that 50% of subjects had abnormal chromosomes, showing premature centromere division of the X chromosome and structural aberrations, translocations, or deletions that could suggest preferential breakpoints. Cytogenetic abnormalities were more common in patients with high frequency of relapse or with progressive MS.

- 5 M. Sandberg-Wollheim, U. Kristoffersson, N. Mandahl and B. Hogstedt, *Increased frequency of chromosome aberrations in long-term cultured cerebrospinal fluid lymphocytes of patients with multiple sclerosis*. J Neurol Sci, 1991. **102**(1): p. 46-50. PubMed ID: 1856732.

A study of 23 MS patients found more chromosomal aberrations in CSF lymphocytes than in peripheral blood lymphocytes (6.4 vs. 4.1;  $p = 0.003$ ). No such difference was seen in nine patients with other neurological diseases or in eight healthy controls. CSF lymphocytes from MS patients had more aberrations than those of healthy controls ( $p = 0.012$ ) but no such difference was found in PBLs. Patients with other neurological diseases and controls were similar to each other in levels of aberrations.

- 6 I. Petcu, D. Savu, A. Vral, H. Thierens, G. Nagels and L. De Ridder, *Chromosomal radiosensitivity in secondary-progressive multiple sclerosis patients*. Int J Radiat Biol., 2004. **80**(9): p. 663-72. PubMed ID: 15586886.

This study found no difference in the occurrence of spontaneous chromatid breaks between MS patients and healthy individuals. However, the mean spontaneous micronucleus yield was higher in MS patients than in healthy individuals. Increased radioresistance was found in MS lymphocytes under a low-dose radiation assay, potentially indicating an enhanced repair mechanism.

- 7 R. Seshadri, G. R. Sutherland, E. Baker, R. Kutlaca, D. Wigmore and A. A. Morley, *SCE, X-radiation sensitivity and mutation rate in multiple sclerosis*. Mutat Res, 1983. **110**(1): p. 141-6. PubMed ID: 6865993.

SCE was increased in the lymphocytes of 34 MS patients compared to controls. However, no increase was seen in X-radiation sensitivity or in 6-thioguanine-resistant mutant cells.

8 Vijayalaxmi, M. S. Newton, C. M. Steel, H. J. Evans and B. Pentland, *Spontaneous and mutagen induced sister chromatid exchange in multiple sclerosis*. J Med Genet, 1983. **20**(5): p. 372-6. PubMed ID: 6417337.  
Spontaneous SCE was about 50% greater in the lymphocytes of 9 MS patients compared with 9 controls. Levels of SCE were increased slightly more in MS patients compared to controls when exposed to mutagens mitomycin C or ethyl methane sulfonate in vitro. However, the authors observe that this may reflect initial basal differences between the cell types rather than hypersensitivity to mutagens of MS cells.

9 J. M. Trader, K. Warecka and E. Schwinger, [*Sporadic and familial-occurring multiple sclerosis. HLA typing and study of chromosomal sister chromatid exchange rate*]. Fortschr Neurol Psychiatr, 1985. **53**(4): p. 134-7. PubMed ID: 3997038.  
This study of 17 MS cases and 10 controls found a significant increase of the SCE rate in sporadic cases of MS but not in patients with familial MS.

10 N. T. Karki, J. Ilonen and M. Reunanen, *Increased sister-chromatid exchange rate and its regression during prolonged incubation in lymphocyte cultures from patients with multiple sclerosis*. Mutat Res, 1986. **160**(3): p. 215-9. PubMed ID: 3485765.  
Peripheral venous blood lymphocytes from MS patients cultured for 72 hours in the presence of phytohemagglutinin appeared to have a higher SCE rate than cells from matched controls. The SCE frequency in patients matched that of controls when the incubation time was prolonged to 9 days by adding interleukin-2 to the cultures.

11 M. Senecal-Quevillon, P. Duquette and C. L. Richer, *Analysis of sister-chromatid exchanges (SCEs) in familial and sporadic multiple sclerosis*. Mutat Res, 1986. **161**(1): p. 65-74. PubMed ID: 3702896.  
SCEs were increased in 17 MS patients vs. 16 controls ( $p = 0.0002$ ) even when considering only those patients not taking medication ( $p = 0.038$ ). This finding suggests that increased SCEs may be a feature of the disease.

12 L. O. Badalian, N. A. Malygina, G. N. Dunaevskaia, A. Ermakov and A. N. Kosichenko, [*Chromosome instability in multiple sclerosis*]. Zh Nevropatol Psikhiatr Im S S Korsakova, 1987. **87**(2): p. 206-8. PubMed ID: 3577508.  
An elevated SCE rate in MS patients vs. controls was confirmed (mean numbers of SCE per cell was 10.5 in patients vs. 8.2 in controls).

13 E. M. Gipps and C. Kidson, *Cellular radiosensitivity: expression of an MS susceptibility gene?* Neurology, 1984. **34**(6): p. 808-11. PubMed ID: 6539446.

Cellular radiosensitivity of T lymphocytes, B lymphoblastoid cell lines and fibroblasts was increased in 40 MS patients compared to controls as measured by radiation-induced chromosome aberrations. The authors suggest that this radiosensitivity may have a basis in autosomal dominant inheritance (judging by patterns among first-degree relatives of MS patients) and may be due to mutations of DNA-processing that predispose to MS.

- 14 P. Sola, E. Merelli, P. Faglioni, D. Monti, A. Cossarizza and C. Franceschi, *DNA repair, sensitivity to gamma radiation and to heat shock in lymphocytes from acute, untreated multiple sclerosis patients*. J Neuroimmunol, 1989. **21**(1): p. 23-9. PubMed ID: 2908880.

No significant difference in DNA repair and survival was found between 15 MS patients and 15 controls after exposure of PBLs to high and low gamma ray doses (2-12 Gy and 100 Gy) and high temperatures (37-45 degrees C). The authors state that genomic instability may be of viral origin and not due to genetic defect in repair of DNA in MS patients.

- 15 O. Vladimirova, J. O'Connor, A. Cahill, H. Alder, C. Butunoi and B. Kalman, *Oxidative damage to DNA in plaques of MS brains*. Mult Scler, 1998. **4**(5): p. 413-8. PubMed ID: 9839301.

The oxidative marker 8-OH-dG was found to be elevated in MS plaques compared to normal appearing white matter. It was also found to be elevated in normal appearing cortical tissues in the vicinity of plaques compared to control cortical tissue. The authors suggest that irreversible degeneration may result from DNA damage due to reactive oxygen species and NO produced during inflammatory episodes.

- 16 D. C. Chen, J. Saarela, R. A. Clark, T. Miettinen, A. Chi, E. E. Eichler, L. Peltonen and A. Palotie, *Segmental duplications flank the multiple sclerosis locus on chromosome 17q*. Genome Res., 2004. **14**(8): p. 1483-92. Epub 2004 Jul 15. PubMed ID: 15256512.

A region on chromosome 17q that contains an MS-associated haplotype was determined to be flanked by duplications and palindromic sequences that may contribute to genomic instability at this location.

- 17 F. X. Weilbach and K. V. Toyka, *Does Down's syndrome protect against multiple sclerosis?* Eur Neurol, 2002. **47**(1): p. 52-5. PubMed ID: 11803193.

Survey of medical literature for references to comorbidity of Down Syndrome and MS found only one case out of an expected 102 in Western Europe, indicating a factor protective against MS on chromosome 21.

- 18 R. P. Roos, *B-cell abnormalities in multiple sclerosis. A hypothesis*. Arch Neurol, 1985. **42**(1): p. 73-5. PubMed ID: 3871325.

This paper suggests that B-cell abnormalities (genetic translocations and abnormalities in the developmental immunoglobulin rearrangements) lead to oligoclonal bands.

- 19 A. Ermis, T. Hopf, R. Hanselmann, K. Remberger, C. Welter, S. Dooley, K. D. Zang and W. Henn, *Clonal chromosome aberrations in cell cultures of synovial tissue from patients with rheumatoid arthritis*. *Genes Chromosomes Cancer*, 1993. **6**(4): p. 232-4. PubMed ID: 7685626.

A variety of structural chromosome aberrations was found in cell cultures of synovial tissue of each of seven patients with rheumatoid arthritis. Trisomy 7, the only recurrent anomaly, was found in six of the seven cultures.

- 20 K. R. Weiss, H. I. Georgescu, S. M. Gollin, R. Kang and C. H. Evans, *Trisomy 7 in synovial fibroblasts obtained from arthritic joints*. *Inflamm Res*, 1999. **48** Suppl 2(p. S132-3. PubMed ID: 10667850.

Trisomy 7 incidence was statistically elevated in freshly isolated synovial fibroblasts of patients with rheumatoid arthritis and osteoarthritis compared to nonarthritic subjects.

- 21 R. W. Kinne, T. Liehr, V. Beensen, E. Kunisch, T. Zimmermann, H. Holland, R. Pfeiffer, H. D. Stahl, W. Lungershausen, G. Hein, A. Roth, F. Emmrich, U. Claussen and U. G. Froster, *Mosaic chromosomal aberrations in synovial fibroblasts of patients with rheumatoid arthritis, osteoarthritis, and other inflammatory joint diseases*. *Arthritis Res*, 2001. **3**(5): p. 319-30. PubMed ID: 11549374.

Chromosomal aberrations (e.g., aneusomies) were found in synovial fibroblasts (SFB) of patients with rheumatoid arthritis, osteoarthritis, and other rheumatic diseases; such aberrations were almost entirely absent from PBLs and skin fibroblasts from the same patients and from SFB of normal joints and patients with joint trauma. This evidence suggests that chromosomal abnormalities are a result of chronic inflammatory stress.

- 22 F. Tascioglu, B. Durak, C. Oner and S. Artan, *Trisomy 7 in synovial fluid cells of patients with rheumatoid arthritis*. *Rheumatol Int.*, 2005. **25**(8): p. 571-5. Epub 2004 Jun 25. PubMed ID: 15221280.

Trisomy 7 was found in 23% to 48% of the synovial fluid cells provided by 8 of 15 rheumatoid arthritis subjects. No trisomic 7 cells were found in the control cases. No monosomy or trisomy 5 was detected in any of the samples analyzed.

**Terms searched in conjunction with “multiple sclerosis”:**

aneuploid/y  
euploid/y  
triploid/y  
monosomy  
disomy  
trisomy  
ring chromosome  
translocation  
chromosome/al aberration/s  
chromosome/al abnormality/ies  
chromosome/al break/s  
fusion gene

chromosome  
chromosomal  
SCE  
chromatid